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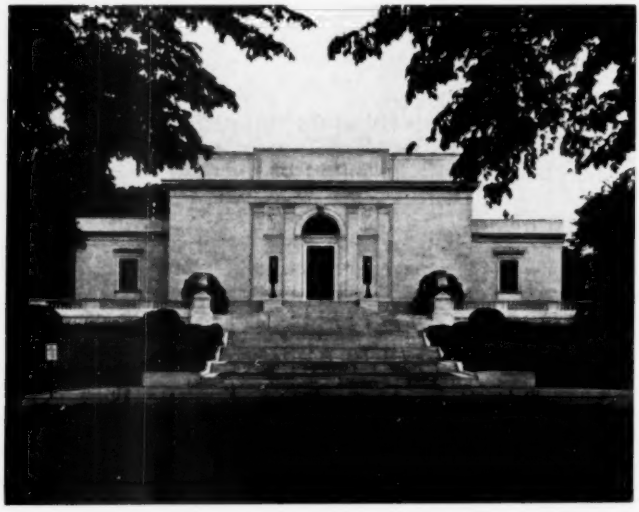

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E D I T O R I A L

PHARMACY'S STAND ON COMPULSORY NATIONAL HEALTH INSURANCE

THE official statement of the American Pharmaceutical Association on the subject of compulsory national health insurance should be read by all pharmacists. Not only is it the official stand taken by the A. Ph. A., but, we believe, it is also the stand taken today by the vast majority of thinking people throughout the United States. In essence this official statement recognizes the need for improving the medical services in this country but it condemns the adoption of a compulsory insurance plan. It is felt that such a socialistic scheme not only might impair our present system of medicine but also serve as an entering wedge for related movements tending to socialize many of our industrial and professional fields.

Those who attended the convention of the A. Ph. A. in Jacksonville had an opportunity of hearing a representative of the Federal Security Agency speak in behalf of Mr. Oscar Ewing's plan, a representative of the American Medical Association speak against it and a representative of the American Hospital Association give the views of his organization. None was impressive except the latter. The F. S. A. representative, as might be expected, repeated the well known arguments for the plan. It was obvious that he, like many others in our nation's capital, believes that a welfare state is our only hope for progress. Were we to follow such leaders we would soon become completely regimented and directed from "the cradle to the grave." We might have security of a sort but it would be security such as that enjoyed in prison where, indeed, little harm can befall us. The fact overlooked by many who seek this security so avidly is that it is purchased only at the cost of liberty. Surely man's history shows that liberty has always been his most valuable possession. The thing which caused our forefathers to come to this new land and which they gained at such great cost should not be so easily surrendered.

We can forgive those in the F. S. A. who argue for compulsory health insurance for it would greatly enlarge their agency and its power over our lives and it is only human to crave power and prestige. It would be foolish for an enlightened people to permit it to happen and we shall not.

The representative of the American Medical Association made an emotional and impassioned attack on Mr. Ewing's plan and those endorsing it. This was a normal and an entirely understandable human reaction. The medical profession in this country has done and is doing a splendid job, all Washington propaganda to the contrary. It is not easy for men like American physicians, who have always been held in high public esteem, to hear themselves denounced in high places and even have their motives and ethics questioned. It is indeed a nasty business for political propaganda to be directed against an old and venerable profession which has served mankind throughout the ages. We can excuse the A. M. A. representative for being aroused and finding it difficult to present his case in the same quiet manner as he might conduct a clinical conference.

The representative of the American Hospital Association was lucid and logical. He acknowledged the need for improving medical services in the country but recommended that it be done by improving what we have rather than by destroying them. Figures were given showing that Blue Cross subscribers have risen in numbers from 3 million in 1939 to 33 million this year. Blue Shield, which is relatively new, already has 10 million members. Such plans were described as consistent with our concept of freedom and private initiative. The role of the federal government was felt to be necessary in the improvement of existing hospital facilities and in aiding medical education, although it was believed that the medically indigent should receive sufficient federal or state aid to give them necessary medical attention.

These views are reasonable and entirely workable and they are in essence those behind the A. Ph. A. stand on compulsory national health insurance.

We, in America, are faced with the necessity of deciding not just the issue of compulsory health insurance but the road which we are to travel in the years ahead. Is it to be a democracy based upon individual initiative and effort or state socialism where controls and regimentation plan for and direct the individual as the state wishes?

Those, who see in state control a better life, must have but little of that early pioneer blood of our forefathers—men who left the old world with its iron clad system of controls to found a new nation based on freedom and liberty. America is the last stronghold of liberty. Whether we maintain it at all costs or fritter it away in search of promised security shall determine not only our future but the destiny of all mankind.

L. F. Tice

IN VITRO EFFECTS OF METABOLITE DISPLACERS ON PSEUDOMONAS AERUGINOSA

By Gustav J. Martin, D. Sc. and Jack N. Moss *

FEW compounds have been found which exert pronounced inhibitory effects on *Pseudomonas aeruginosa.* Sulfonamides (1), (2), (3), show slight inhibitory action. Heinemann and Blanchard (4) tested a mercurial, 2-acetoxy-mercuri-4-diisobutylphenol, which was active up to a concentration of 1:5,000. Lawrence (5) has reported certain derivatives of *p*-aminomethylbenzene sulfonamides which exert bacteriostatic effects. Barber and Haselwood (6) have shown *o*-aminophenol to be bacteriostatic against *Pseudomonas aeruginosa.*

Studies of the chemotherapy of *Pseudomonas aeruginosa* became of importance due to the ever increasing incidence of infection and the lack of effective agents against these infections (8).

Experimental

Varying concentrations of each agent, which had been previously sterilized, were aseptically added to tubes containing the synthetic medium of Burton et al. (7). Each tube was then inoculated with one drop of a 24-hour culture of *Pseudomonas aeruginosa,* strain 9027 (A. T. C. C.) grown in the same medium. After incubation at 37°C for 24 to 48 hours each tube was strongly shaken to afford as uniform a suspension as possible. The results were read turbidimetrically. The test was run in duplicate or triplicate tubes, with appropriate controls.

Results and Discussion

The following compounds did not inhibit the growth of the organism: 5-methyltryptophan, *o*-methyltyrosine, N-methyltyrosine, 3-methyltyrosine, β-(2-benzothiophene)-α-aminopropionic acid, salicyoyl β-alanide, salicyluric acid, *o*-fluorobenzoic acid, pyridine-β-sulfonamide, ethionine, methylfolic acid and methionine sulfoxide.

* Research Laboratories, The National Drug Company, Philadelphia, Pa.

Table I presents an outline of the compounds which were effective in inhibiting growth of the organism. The approximate concentration bringing about a 50% inhibition is given (M. E. C. 50).

TABLE I

COMPOUNDS EXERTING AN INHIBITORY EFFECT ON *Pseudomonas Aeruginosa*

Compound	*M. E. C. 50*
9-Aminoacridine HCl	0.02 mg. per ml. 36 hours
p-fluorophenylalanine	0.025 mg. per ml. 48 hours
α-amino-isobutane sulfonic acid	0.5 mg. per ml. 24 hours
Imidazole-aminomethyl-sulfonic acid	1.0 mg. per ml. 24 hours
Phenylserine	1.0 mg. per ml. 24 hours
2-Isopropyl-5-methylphenoxyethyl-diethylamine HCl	0.1 mg. per ml. 24 hours
Pyrithiamine	1.0 mg. per ml. 24 hours
Benzoxazolone	0.5 mg. per ml. 24 hours
N-sulfanilyl-4-aminobenzimidazole	0.5 mg. per ml. 24 hours

As shown in Table I the most pronounced effects were produced by 9-aminoacridine and *p*-fluorophenylalanine. However, it should be mentioned that the activity of the former was present for about 36 hours, whereas the latter exhibited bacteriostatic effects for at least 48 hours. Since the effect of *p*-fluorophenylalanine was exerted over a longer period of time than any of the other agents, it was assumed that the activity was brought about by interference

with a more important "metabolite" which the organism was synthesizing; probably phenylalanine.

This was readily demonstrated by testing the effect of *p*-fluorophenylalanine in the presence of varying amounts of phenylalanine (Table II).

TABLE II

THE EFFECT OF PHENYLALANINE ON *Pseudomonas aeruginosa* GROWTH INHIBITION BY *p*-Fluorophenylalanine

dl-Phenylalanine mg/ml	*p*-Fluorophenylalanine mg/ml	Photometer Readings
0	0	140
0.1	0	170
1.0	0	220
0	0.001	145
0	0.01	85
0	0.1	22
0	1.0	*
0.1	0.001	170
0.1	0.01	168
0.1	0.1	155
0.1	1.0	20
1.0	0.001	220
1.0	0.01	215
1.0	0.1	210
1.0	1.0	150

* Complete inhibition

The inhibition of Pseudomonas, produced by the *p*-fluoro-compound is counteracted by phenylalanine. The results above show that phenylalanine exerts a marked enhancing effect on the growth of the organism.

Studies *in vivo* are warranted with compounds of this type as they might well be an important factor in chemotherapy of infections by Pseudomonas.

Summary

1. A series of metabolite displacers were tested for antibacterial activity against *Pseudomonas aeruginosa*.

2. From the group tested, the following compounds exhibited inhibitory properties: 9-aminoacridine, *p*-fluorophenylalanine, α-aminoisobutane sulfonic acid, imidazoleaminomethyl sulfonic acid, phenylserine, 2-isopropyl-5-methylphenoxyethyldiethylamine HCl, pyrithiamine, benzoxazolone and N-sulfanily-4-aminobenzimidazole.

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THE PROFESSIONAL PRACTICE OF PHARMACY *

By Samuel W. Goldstein Ph. D.**

IT IS a great honor and a happy privilege to address this select group of outstanding professional pharmacists. I am convinced that, because this Society of the American College of Apothecaries exists and will grow, pharmacy has a better chance of deserving the recognition and respect extended to professional groups. The recognition earned by this particular group must need be tremendous to carry some of our brethren into the desired land of professional recognition. This is extremely difficult when too many pharmacists exhibit no concern about their professional duties and are millstones about the necks of those who carry the torch of professionalism.

The title of this paper is "The Professional Practice of Pharmacy." That title is used advisedly rather than the more common title "The Practice of Professional Pharmacy." This is not a matter of quibbling with words. The question of whether pharmacy is or is not a profession is answered by the manner in which the individual carries on his practice. While a professional atmosphere and limitation of duties to pharmaceutical activities are conducive to professional practice; still the individual pharmacist can, if he so desires, practice pharmacy professionally in other types of the modern drugstore.

It is customary to deliver talks about professional pharmacy to student groups. Practicing pharmacists are usually subjected to lectures about how to display goods, and other means for increasing turnover and income. I heard one on how to dip ice cream profitably. I hope that such lectures have been successful and that pharmacists are making almost all the money they want. As some of you know, it is my hope that several of the general practices of pharmacists, especially as they pertain to compounding activities, will be altered. I would also like to see a proper fee system developed for compounded products. The fees should be large enough to compensate for careful compounding procedure. I take advantage of every opportunity to emphasize to non-pharmacists, the important role of pharmacy in the medical care program. But there is one phase of pharmacy that I discuss only with my brother pharmacists. This is it.

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* Presented at the 1949 Convention of The American College of Apothecaries at Jacksonville, Florida.

** Pharmaceutical Chemist, Maryland State Health Department, Member of American Pharmaceutical Association Committee on Prescription Tolerances.

There are many pharmacists who conscientiously feel that they exercise sufficient care in their compounding; because, to their knowledge, no ill effects attributed to their compounding have been reported in the patients who have used their products. When a pharmacist accepts a prescription and approves the dosage requested thereon, he assumes the solemn obligation to dispense exactly what the physician has ordered. This phase of pharmaceutical ethics has been preached by the American Pharmaceutical Association, the National Association of Retail Druggists, and the other national as well as the state and local pharmaceutical associations. That has been a fine undertaking, and notable results have been achieved. But the interpretation of "*exactly* what the physician has ordered" has been too greatly restricted to "no substitution." That "*exactly*" also means: as near the requested quantity and dosage as is possible by means of reasonable care and proper compounding technique. The general welfare and the public health would benefit to a greater extent if the combined efforts of all pharmaceutical organizations were now directed toward the implementation of the latter interpretation.

"The present growth of local and state public health laboratories tends toward more strict supervision of compounded pharmaceuticals. The Sullivan case decision of the Supreme Court practically invites the Federal Food and Drug Administration to start checking on the products of the 60,000 prescription-counters in this country. We must set our own house in order if we wish to avoid being subjected to degradation, loss of prestige, and ridicule. And let me tell you in all solemnity and with all the emphasis at my command that, no matter which section of the pharmacists of this country may be selected for checking purposes, the same sorrowful results will be obtained by investigators. We cannot afford to play ostrich and hope that no one else will see our faults. Others have already seen them and have gone so far as to expose them in the public press. Until a few years ago, such criticism had been periodic. We can now expect it to be continuous.

The modern era of drug standardization started with the enactment of the Food and Drug Law of 1906. The modern era of critical study of compounding precision started with the U. S. Public Health Service effort (Wilbert) in 1913. The Federal Food and Drug Administration study of 100 prescriptions compounded in Washington, D. C. in 1932 resulted in much criticism and unfavorable publicity.

It also instigated the establishment by the A. Ph. A. of the Committee on Prescription Tolerances to study the causes of compounding deviations and to determine, if possible, reasonable limits of error for prescription-counter products.

Pharmaceutical educators cannot execuse themselves with the thought that the errors made at the prescription-counter are made only when the pharmacist neglects to follow the lessons he learned at school. The educators must teach the pharmacist not to neglect those lessons. And the Boards of Pharmacy should be authorized to select proper pharmacies for student and graduate internship. If necessary, reduce the hours of instruction of less essential material and include a course on the ideals and ethics of pharmacy. Or include such a course in the longer curriculum being considered. Dean Little declared that the big challenge before our professional colleges today is to impart more wisdom and, perhaps, fewer facts to the students. More and more is said of teaching the necessary courses to enable the pharmacist to run his store profitably, in the sense that he will accumulate material wealth. Let more and more be said of the great wealth of satisfaction that can be part of the professional heritage of pharmacy. We all remember pharmacists who lived and worked for their fellow men; we remember their appearance, their bearing, their attitude; we remember them with pride. In this particular group, we need not depend upon our memories, we can look about us and see such men.

I do not mean to imply that compounding precision was greater twenty, or thirty, or fifty years ago than it is today. I believe that pharmacy today is giving an important and good overall service to the U. S. public. But that public demands all that was given before and starts from there with a whole new set of demands. One of those demands; the demand for precise work, we cannot ignore; inasmuch as a group we desire professional recognition on the basis of our scientific training and service. It is right to expect that as our educational standards are raised, our compounding precision should increase. Perhaps it has to some extent, but it definitely has not increased sufficiently.

Some pharmacists at the San Francisco A. Ph. A. Convention seemed to react violently to any suggestion of criticism that did not first condemn the dispensing physician. Such persons should hesitate before throwing verbal brickbats. Those things sometimes

bounce. Dr. O. H. Howe, in 1913, made the following statement: "No physician should jeopardize his patients or his own reputation by relying on a prescription service which he knows to be poor. If necessary, he should provide and dispense his own medicine." ". . . it (the modern drugstore) cannot and should not be relied upon as a source of reliable medicines. The well-equipped and conscientious druggist who has a high standard of work and lives up to it should be encouraged." I disagree with some of his reasoning, because you can find many well-equipped and conscientious druggists operating modern drugstores. Nevertheless, enough evidence has been published in the last three years to supply fresh ammunition for another blistering attack from those gentlemen. In 1913 the House of Delegates of the American Medical Association passed a resolution to bring the matter of unreliable drugs to the attention of the federal and state drug law enforcement authorities, and to urge on them the need for more energetic and effective enforcement of drug standards. Those authorities no longer need urging. All they need are men and money. It is up to the pharmacists to see to it that the drug standards that are enforced are reasonable and equitable standards.

Lyman F. Kebler, in 1913, noted the variations in the constituents of Iodine Tincture purchased in drugstores. He wanted to know if there was any substantial reason for . . . the (excessive compounding) variations? And he said: "The permissible variation from the standard must be met sooner or later. Shall it be stringent or reasonable? If reasonable, shall the variations be 5 per cent, or 10 per cent, or 20 per cent?" The pharmacists evaded that particular challenge by utilizing the manufactured product. And the answer to the question "What is a reasonable standard"? was not offered until 1948. Until now, all the public criticism of prescription-counter precision has been based upon stringent interpretation of the existing offical standards. I believe this has been a false and misleading basis of criticism. Work has been done in an effort to develop reasonable and equitable standards of tolerance for prescription-counter products. I believe the basis for their establishment has been found. But don't expect too much from reasonable standards. They may alter the brutal edge of the criticism, but the edge will still be sharp enough to cut our professional pride to tatters in the eyes of discerning individuals.

The latest study of compounding precision represents the first attempt to evaluate this phase of pharmaceutical practice on a national and international scale by means of a spot-check survey of the United States and Canada. This survey was just completed, and I can tell you that the situation it discloses is not one to make the professional pharmacist very happy.

One of the results of the survey of compounding precision should be especially interesting to this group. For some time it has been argued that the best type of pharmacy for the public good and the pharmacists' welfare is the professional pharmacy requiring the service of at least two pharmacists. Arguments and data have been presented to show that such establishments are most profitable to the operators. The limited data accumulated during this survey present the first proof, to my knowledge, that these establishments offer the public more precisely compounded products.

Here is a summary of the data: Seventy-three per cent of the 48 samples of 3% Boric acid solutions purchased in professional pharmacies meet the ±15 per cent tolerance assigned by the system appearing in the March issue of the Scientific Edition of the A. Ph. A. Journal. Sixty per cent of the solutions purchased in 343 other drugstores meet the same tolerance. On the basis of a ±10 per cent tolerance, which some drug officials declare is a liberal tolerance, 63 per cent of the professional samples and only 49 per cent of the others could qualify for acceptance. Elimination of the 3 stock solutions dispensed in professional stores, allows acceptance of 79 per cent of the extemporaneously compounded Boric acid solutions, using the 15 per cent tolerance.

Of the 43 samples of 2% Neo-Silvol solution purchased in professional stores, 88 per cent meet the 15 per cent tolerance. Seventy per cent of the solutions purchased in 373 other stores meet the same tolerance. A 10 per cent tolerance lowers the acceptance to 72 per cent and 55 per cent respectively.

Results with a 2% Phenol in Oil solution are enlightening. Sixteen samples were obtained from professional stores, and 75 per cent meet the allowed 20 per cent tolerance. Only 44 per cent could meet a 10 per cent tolerance. Eleven samples were purchased at other stores. One sample meets the 20 per cent tolerance. Five samples show deviations exceeding 50 per cent.

It is clearly evident that the use of a 10 per cent tolerance for all compounded solutions is unsound and unreasonable. The fact that most of the solutions that do not meet the proposed tolerances show extremely wide deviations indicates that these tolerances are reasonable and equitable.

I believe that the greater benefit from official reasonable standards for prescription-counter products will result from the awareness of the pharmacists that there *are* standards which must be met in compounded preparations. This will affect most those pharmacists who now feel (and rightfully so) that no specific standards exist for such work, and who wrongfully allow that feeling to lead them in the path of carelessness. If some of those brothers could be brought back to the green pastures of careful compounding, the pharmaceutical group would have cause for rejoicing.

The biased critic will deny to the whole pharmaceutical group the praise that is its due for the splendid contribution it has made and is making toward the health and happiness of the people of this nation. The fair critic will offer that praise in good measure, but not in full measure; for, in truth, it is time that the body pharmaceutic expunged the viper of carelessness from its professional bosom. It can be done, and it must be done, before we can honestly claim that we, as a group, practice the art and the science of pharmacy. I have friends whom I regard highly as men and as professional pharmacists. Some of them conduct so-called professional pharmacies and some operate general merchandise enterprises along with their professional work. Going back a way we can cite an outstanding example of an ethical dealer in merchandise. Who can think of Benjamin Franklin other than as a great and good man of high ideals who adhered to a strict code of ethics? Still, among many other things he handled in his store on Market Street, Philadelphia, were such things as chocolate, mustard, saffron, copper stills, spermaceti, palm oil, patent medicines, spectacles, and lottery tickets. Let us not forget that, while there is much to gain in financial returns and economic security from a successful merchandising effort, an even greater personal and social satisfaction can be ours. The knowledge that we have served our fellow men to the best of our abilities in our particular field of endeavor is the privileged blessing of the professional pharmacist.

BASIC RESEARCH PROGRESS IN THE FIELD OF DERMATOLOGIC DISORDERS *

By Howard T. Behrman, M. D.**

DURING the past few years, great strides have been made through the medium of basic research in the therapy of dermatologic disease. Many diseases hitherto classified as either incurable or extremely recalcitrant to all forms of therapy have responded almost miraculously to new drugs or to newer modifications and methods in the use of older remedies. The modern dermatologist, smarting under the appellation often attached to his specialty, namely "they never kill nor cure," has come forth with many cures for the more superficial ills of mankind. In a short paper of this type, it is possible to discuss but a few of the more important advances in this field. For the purpose of this report, the therapeutic armamentarium in dermatology has been roughly subdivided into a) drugs taken internally, and b) drugs applied topically.

Let us first consider several drugs taken internally for external disease. One of the most important of these groups is the antihistaminics. These drugs are of primary value in the treatment of allergic disease, although the tendency at present is to employ them as a panacea for all the cutaneous ailments to which the flesh is heir. As might be expected, they will not perform miracles, but they do have a definite and specific value.

They are effective primarily in the treatment of acute urticaria, and to a lesser extent chronic urticaria. This effect is unrelated to the cause of the eruption and will be of equal value in the urticaria from food such as shellfish and strawberries as in the frequent eruptions following drugs, especially penicillin. To a lesser extent, the antihistaminics are effective in various physical allergies and forms of pruritus. Unfortunately, at the present time, the appearance of the symptom of itching in the patient seems to evoke a conditioned reflex on the part of the doctor. As with Pavoly's dogs, the itch is the

* Delivered at the mid-year convention of the American Pharmaceutical Manufacturers' Association, in the Waldorf-Astoria Hotel, Dec. 6-8, 1948.

** Assistant Clinical Professor of Dermatology, New York University College of Medicine.

ringing bell which stimulates not saliva but the prescription of an antihistaminic cure-all. It must be realized that itching is the most common symptom encountered in dermatologic practice and may be observed in at least fifty organic diseases and several hundred cutaneous disorders.

The antihistaminics are a group of substances which, in principle of action, resemble the antibiotics. In the allergic conditions in which antihistaminics are used, theory has it that histamine is produced and acts upon the cells that are sensitive to it. Administration of the antihistaminics interferes by biological competition with this action of histamine, thus making its effects null and void. Staub and Bovet first reported two chemical compounds with marked antihistaminic and antianaphylactic properties. These compounds, however, were too toxic for clinical use. These substances, however, had properties which made them of great value in the treatment of allergic disorders, and research developed products having the same properties, but in which the toxic properties were greatly reduced. It is true that today we have many effective antihistaminics which are in popular use, but we still have not attained perfection. There is still room for improvement in the production of such compounds having even greater antihistaminic properties and still lower toxic and adverse side effects. Along the same lines of specific interference between two substances, whether chemical or biological, we have the recent discovery of dimercaprol, the British Anti-Lewisite (BAL), in the treatment of arsenical poisoning. Important as this discovery is in the treatment of such conditions as exfoliative dermatitis, the principle involved is of even greater interest, for it propounds the idea that once the cause of a condition is known, the cure may then be sought after. If we can just continue a step further along these lines of fundamental and basic study of the mechanism of disease, it may be not far in the future that we will possess remedies to cure psoriasis, acne vulgaris and similar diseases. In this connection it is of importance to keep in mind that each type of disease is a biological reaction carried out through a series of enzymatic processes, each one of which may be interfered with by some specific chemicals, just as is true for histamine, for arsenic or for certain bacteria. By the same token, it is quite possible that many of the allergic manifestations which are not responsive to the antihistaminics are probably due, at least in part, to a hyaluronidase type of reaction. It may prove fruitful for the derma-

tologist and allergist to investigate drugs along this line—to discover a series of antihyaluronidases. In explanation, it may be stated that in response to injury, the tissue, especially that of the skin, liberates several kinds of substances. Some of these are (1) histamine, (2) leukotoxin, (3) potassium ions flowing outward from the cells into intercellular spaces, and (4) the liberation of hyaluronidase or the spreading factor. The latter is an enzyme first found in testes and has the power of hydrolyzing hyaluronic acid, a mucoid complex made up of pentose sugars. When this occurs, the spread of materials within the skin is facilitated, thus, protein penetrates into the tissue, bacteria toxins and dyes penetrate much faster, and thereby satisfy all of the criteria for inflammation. This may be the reason why the antihistaminics are not specific for all types of inflammation. It may be hypothecated that where the inflammatory reaction is due primarily to the liberation of histamine, as appears to be the case in urticaria, the antihistaminics are virtually specific. On the other hand, in the type of inflammation observed with poison ivy dermatitis where the antihistaminics are minimally effective, it may be that histamine is liberated minimally and hyaluronidase maximally. Until we have a drug which for convenience we may call an antihyaluronidase, specific proof of this contention will be difficult to obtain.

A brief discussion of chemotherapy and the antibiotics will suffice because of their limited sphere of usefulness in skin disease. The sulfonamides are used in dermatologic practice primarily in the diseases of chancroid and dermatitis herpetiformia. Penicillin is of exceptional value in syphilis and in infections such as carbuncles and erysipelas. Streptomycin is effective in granuloma inguinale, bacitracin in the local treatment of surgical infections, and aureomycin in lymphogranuloma venereum. The list is actually as small as that. The external application of these remedies is generally not advised by the dermatologist as a protective measure for the patient. The reason for this decision lies in the fact that whereas the sulfa drugs and the antibiotics are effective in the treatment of various superficial infections and minor disorders, they are also capable of inducing many forms of local or systemic allergic reactions and various undesirable side effects. This has become increasingly evident with their indiscriminate use. The development of hypersensitivity to these agents because of their injudicious use for some minor illness or trivial skin disease might preclude a later systemic administration where life or

death hangs in the balance. We believe that superficial skin disease should be treated with either older or newer remedies which are not apt to be used systemically in the future for serious illness. The only exceptions are those cases wherein the antibiotic drugs are either significantly superior to other safer remedies or where these safer remedies cannot be employed for various specific reasons. In other words, in dermatology we are prevented from taking advantage of the forward march in chemotherapy by this restriction of possible sensitization. This fact certainly affords an opportunity for outstanding advances in such therapy, as, if and when antibiotics are available which may be freely used without fear of sensitization. At the present time the prime objective appears to be the production of antibiotics with higher and higher antibiotic activity. Our researchers should also take into very serious consideration the production of antibiotics with lower and lower sensitizing properties. The recent development of dihydrostreptomycin hydrochloride is a step in this direction.

One of the most remarkable discoveries of the war period is the drug dimercaprol or B. A. L., an abbreviation for the term British anti-Lewisite. This discovery by Stocken and Thompson from R. A. Peters Laboratory, stemmed from various attempts to neutralize the severe local and systemic effects of the vesicant war gases in the event of their use by the Germans. It was known that the toxicity of lewisite, one of the most active vesicant gases, and of trivalent arsenicals in general was due to their ability to combine chemically with the essential -SH (thiol) groups of certain cell proteins (especially the pyruvate oxidase system) to form stable compounds. These combinations inactivated the chemical enzymes and groups essential for basic cellular respiratory function and for life itself. Simple dithiol compounds, of which BAL is one of the most effective and least toxic, have a greater selective affinity for arsenic than do these cell proteins, and thus form a more stable compound with the arsenic. The arsenic is accordingly detoxified and subsequently excreted provided the toxicity is not too long established. This fact has rendered BAL of great value in the treatment of hitherto extremely resistant cases of exfoliative dermatitis and other extensive forms of cutaneous eruptions and systemic disturbances due to poisoning from arsenic, mercury, bismuth and gold. As has been mentioned, BAL is a dithiol compound. Much remains to be learned about the possibilities of the thiols in the treatment of poisoning by various metals. Basic

research in this direction may disclose that other merceptans may prove safer and more effective than BAL itself. Of interest, too, is the fact that the use of BAL presents a philosophy of therapeutic treatment which is not new, but is one which for years has been the objective of important research, namely, of finding specific agents for the treatment of specific ailments. For example, in the treatment of a very common skin disease, namely, poison ivy dermatitis, the best remedy we have available and a poor one at that, is the use of antihistaminics, which may reduce the itching. The active substance in poison ivy dermatitis is toxicodendrol. What is toxicodendrol? There has been some work done on this chemical; there are some ideas as to what it is. Lead salts cause it to precipitate; it oxidizes slowly in the air to an inert substance and so forth. But the field is wide open for research in the endeavor to find a substance which may chemically combine with this active material, and thereby inactivate it, not only in the test tube but in the tissues. The incidence of dermatitis following contact with poison ivy and hundreds of similar substances encountered naturally and in occupational exposures, makes this problem one of major importance and dermatologists certainly would welcome efficient means of treatment.

The treatment of leukemia, Hodgkin's disease and lymphosarcoma has been advanced by the addition of the betachloroethyl amines (the nitrogen mustards) to the other methods of therapy used in the so-called lymphoblastoma group. In this group, the skin disease known as mycosis fungoides has also been treated with this drug. The effects, unfortunately, are usually of temporary value only. Of greater value in radioresistant cases of this disease is the employment of antimony preparations such as tartar emetic and a newer and less toxic pentavalent antimonial. Other heavy metals of recent importance in the treatment of skin disease include a newer, orally administered, form of bismuth, namely sodium bismuth triglycollamate. This drug is of some value in the discoid type of lupus erythematosus but its reputed efficacy in lichen planus and similar diseases has not been proved.

The brilliant strides effected dermatologically in the field of vitamin research and knowledge are at present in partial obscurity due to the vast and frequently uncritical therapeusis in this branch of medicine. A more careful analysis of strictly clinical interpretations and reports of improvement following vitamin therapy in skin

disease might lessen this trend. Results obtained on the skin of animals in the laboratory must be transferred to the human with caution, not only because of the differences in utilization by the animal but due as well to the fact that human skin differs so profoundly from that of other animals in both structure and function that we can learn about it only from studies on human beings. At the present state of our knowledge, certain conclusions can be drawn. Vitamin A is probably of value in increasing skin and mucous membrane resistance and lessening keratinizing metaplasia. Yet a group of nurses (Robertson and Morgan) who took 50,000 I. U. of vitamin A daily for two years had no higher concentration in their plasma than did a control group who had no more than was contained in their diet. Marrack states that within limits, the concentration of vitamin A in the plasma seems to be characteristic of the individual and little effected by intake. The truth of this statement remains to be proved. Vitamin A is advised dermatologically in acne with severe comedo formation as well as in Darier's disease, and other skin disorders characterized by follicular hyperkeratosis. It is more effectively absorbed in aqueous than in oily solutions.

The members of the vitamin B complex series have a limited value in skin disease. The panthothenates and para-amino benzoic acid may influence graying of the hair in rats but perhaps these animals worry more about their diet. At any rate, these substances will not prevent or lessen graying of the hair in humans, probably because these vitamins are never in chronic low supply. However, if there should be a case of a person developing gray hair because of lack of these vitamins, a very remote possibility, it might reasonably be expected that administration of them would prove as curative in the human as in the rat. Very often, vitamins, for this and other reasons, are prescribed on the theory, "What do we have to lose?", but this is a lamentable situation. We should have more conclusive evidence and methods of determining lack of vitamins before we prescribe them. On the other hand, we do know that niacin will cure pellagra, etc., riboflavin will improve certain cases of scaling lips and angular stomatitis and sodium para-amino benzoic acid is of value in some cases of lupus erythematosus and the entire complex may be of value in certain resistant cases of nummular and eczematous dermatitis. It is also recognized that in various subclinical states of vitamin deficiency, the use of various members of the vitamin family may be

the essential means of providing simultaneously both a diagnostic and curative agent.

We next approach the vitamin D group wherein calciferol or vitamin D_2, as originally advanced by Charpy and Dowling promises a great improvement in the treatment of certain cases of tuberculosis of the skin. The vehicle was originally considered of importance but subsequent studies have disproved this belief. This drug produces an acute vascular and leukocytic reaction in lupus tissue with the liberation of tuberculotoxine followed by fibrosis and diminution of the local blood supply. Calciferol is of greater value in the early stages of this cutaneous disease. The patient's urinary and blood calcium levels must be carefully checked during the administration of this drug.

The last vitamin of cutaneous significance is vitamin E. Vitamin E consists of several fat-soluble tocopherols of which alpha, beta, gamma and delta have been isolated in their natural state. Alpha-tocopherol is found in cotton-seed oil and is also produced synthetically; beta-tocopherol is obtained from wheat germ; and gamma and delta tocopherols are derived from soya bean. The natural tocopherols are extracted by vacuum distillation. Burgess employed vitamin E in various collagenosis. He reported specific improvement in lupus erythematosus of all types and even a loss of photosensitivity in the patients. Improvement was also observed in sclerosis of the legs associated with ulcers and to a lesser degree in scleroderma and dermatomyositis. The vitamin actually produced a regeneration of degenerated collagen bundles and a re-formation and rehabilitation of elastic tissue fibers. The author also stated that vitamin E probably affects sebaceous gland activity inasmuch as sebaceous secretion increased under treatment as manifested by the appearance of comedones and a greasy scale. As matters stand, the use of vitamins to treat skin diseases, other than those mentioned and regarded as evidence of some deficiency must remain empirical.

Proteins have also been employed in various skin diseases, and are of some importance. For example, Marrack observed that keratin contains a higher proportion of cystine than is found in most other proteins. Excessive formation of skin keratin may require more cystine than is supplied in the food. Peters found that the scales shed by a man suffering from exfoliative dermatitis contained only three per cent of cystine. The patient had edema and ascites and

was apparently dying. He was cured following administration of cystine. Similar cases (Goldsmith) have recently been observed and specific amino-acids appear to be of value in exfoliative dermatitis, scleroderma, dermatomyositis, pemphigus and infantile eczema (Wolpe). The value of proteins in these conditions is primarily due to their content of from eight to ten so-called essential amino-acids which must be consumed before health may be maintained. So far as the skin is concerned, as in the case cited, the sulfur containing amino-acids such as cystine and methionine are of importance, because the skin and the hair are rich in cystine. Methionine is important because it is a precursor of cystine when cystine is in low supply. It is obvious, therefore, that in conditions where there is much loss of the superficial layers of the skin, the rebuilding of these materials requires a diet rich in sulfur-containing amino-acids. Unless these are furnished, the skin will suffer to the extent of the deficiency. Conversely, a lack of sufficiency of the sulfur containing amino-acids in the diet may result in a breakdown of the skin and of hair growth, resulting in skin disease which can be cured only by furnishing an adequate supply of the building blocks of the protein molecule.

Of increasing importance is the role assumed by the steroid hormones in skin diseases. Our present knowledge has been summarized by Barber in an admirable review as follows:

(1) that androgens stimulate the surface epithelium and the sebaceous glands, tending to produce hyperkeratosis and seborrhea;

(2) that estrogens have a contrary action in that they diminish keratinization and the activity of the sebaceous glands.

The entire problem of growth and distribution of coarse hair, of seborrhea and indirectly acne vulgaris and of dandruff rests basically on these two facts. The comedones of acne probably result from the stimulation to keratinization exerted by androgen, most of which is derived from the glands in male and from the adrenal glands in female. As is known, there is a rise in the excretion of seventeen ketosteroids in females at the time of puberty indicating the increased adrenal activity that accompanies that of the ovaries. The hormonal control of the growth of pubic and axillary hair in females is not primarily dependent upon ovarian functions but upon an

endrogenic hormone derived from the adrenal cortex. Coarse hair on the face, trunk and limbs results from stimulation of hair follicles by androgen. The hair follicles on the vertex and tempero-frontal region of the scalp are exceptional in that growth of the hair in them is stimulated by estrogens and inhibited by androgens; hence the occurrence of baldness of varying degrees in a high percentage of males, and in some females with ovarian insufficiency or virilism and at the climacteric. These basic facts are specific and stimulating but indiscriminate endocrine therapy is fraught with danger in the light of our present day knowledge. The aforementioned facts are of value only in the exceptional case of acne and of alopecia. However, the practical application of endocrine therapy in these diseases is as elusive as the pot of gold at the end of the rainbow and still awaits the applied research of the future.

We now come to a discussion of recent advances in the local treatment of dematologic diseases. The advances in the therapy of these diseases may be divided into (1) the treatment of infections, (2) of animal and vegetable parasitic infestations, and (3) the treatment of certain forms of verrucae. Although many other new local remedies and vehicles have been discovered, these advances were considered of greatest importance. The problem of the destruction of animal parasites on the surface of the skin is no longer a serious one due to the development of DDT and other agents. The development and introduction of the use of DDT occurred during the war. Various other chlorinated compounds have been developed since its advent. Great strides have been made in treatment by the use of these compounds and each day we see new derivatives being developed as toxic agents for various animal parasites. Most of the compounds at the present time are chlorine-containing; possibly other halogens might be used, such as bromine and iodine, with other chemical structures. One of these newer agents is the gamma isomer of hexachlorocyclohexane which should be labelled HCH to follow the present trend of abbreviation, viz. DDT, BAL and so on ad infinitum. This substance has been reported to be practically one hundred per cent effective in the treatment of scabies and all surface animal parasitic disease such as pediculosis without giving rise to any disagreeable side-effects or dermatitis. Combinations of DDT, benzyl benzoate and various wetting agents have also been found to be quite efficient in these diseases but are more apt to produce dermatitis due

to allergic hypersensitivity to one of these ingredients. The field is wide open for continued advances in the development of new, more efficient and less irritating parasiticides.

The vegetable parasites responsible for the superficial fungus infections of the skin have also been subjected to a veritable barrage of new therapeutic weapons. Most prominent in this group are the aliphatic unsaturated fatty acids which were found to be the ingredients in human sweat responsible for its fungicidal activity. These unsaturates include propionic, caprylic and undecylenic acid and their salts. While these substances are fungistatic and fungicidal to a certain extent, they are by no means a cure-all for fungus infections, nor are they as effective in specific instances as some of the older remedies. Their great value lies in their low sensitizing and irritating potential so that they can be used by large cross-sections of the population, both prophylactically and therapeutically without fear of aggravation of the cutaneous disease. It should be emphasized, however, that experience has shown these agents to have a low therapeutic index frequently necessitating the use of more irritating but more effective local remedies. Recent studies have brought to light a more promising group of drugs which appear to be superior in fungistatic and fungicidal action than the aliphatic unsaturated fatty acids. This new group is composed of various quinone and dithiocarbamate derivatives. The dithiocarbamates are superior in respect to toxicity and fungistatic activity; they are not inactivated in the presence of blood as are the naphthoquinones and they are also bacteriostatic. Further studies and clinical trial are in progress on this series in order to evaluate their practical application. Other new fungicides of value are copper salts of the above and salicylanilid. The latter two agents are of particular value in resistant cases of ringworm of the scalp.

Another local remedy of value is podophyllin. This drug has been used in medicine for many years as a vermicide, cathartic and as a local escharotic. Applied topically it cures condyloma acuminata for venereal warts. Podophyllin is effective when dissolved in alcohol or suspended in oil. Its active ingredient has been shown by chemical analysis to be a substance called podophyllotoxin. The cell change produced by this drug suggests inhibition and arrest of mitosis, indicating the possibility of similar parallelism in the study of cancer. It is of little value in the treatment of ordinary verrucae although

it is of occasional merit in resistant types of subungual and plantar warts.

Now a word or two on ivy poisoning, still a major health problem. Prevention or early treatment of this dermatitis by prolonged washing with soap or by the application of chemical agents such as a ten per cent sodium perborate cream are effective only if applied within a few minutes after contact. They are of no value therapeutically. Desensitization procedures are still far from satisfactory. Although there are clinical reports of protection by intramuscular inoculation, the results are questionable. The oral administration of ivy extract over a two month period can produce temporary desensitization with large doses. However, these large oral doses of ivy extract are apt to produce skin eruptions and gastrointestinal reactions especially pruritus ani. From a study of these results, it is probable that the average patient would prefer the disease itself to a severe bout of anal itching. This narrows the outlook down to either avoidances of the plant or its environmental control by means of two new chemical herbicides (ammonium sulfamate and dichlorophenoxyacetic acid) or finally to merely local measure to control the eruption and its subjective symptomatology.

In conclusion, it may be observed from this report that the therapeutics now available are exceedingly few. There is a great need for research in the development of new therapeutic agents, and in determining the cause of dermatologic disturbances. Therapeutic advances can merely parallel the elicitation of fundamental mechanisms of disease and disease processes. I have discussed but few of the external therapeutic agents because the number of actual specific and valuable remedies in this group is very small. So too, the number of skin diseases responsive to these agents is also small. The field is wide open for research in the study of causes of so many of those skin diseases which today are practically unknown, but tomorrow will probably have succumbed to the newer weapons of science.

I have told you of some of the important things that have been done. These are the signposts of the future pointing out the roads to be followed by the searching minds in medicine and in pharmacy where research is to carry us. There is still much to be done in determining the causes of skin diseases and the development of proper therapeutic agents. We have just scratched the surface.

AGRICULTURAL RESEARCH AND PHARMACY

By T. Swann Harding

RECENT APPEARANCE of a Farmers' Bulletin No. 1999 from the Department of Agriculture, Production of Drug and Condiment Plants, by A. F. Sievers, is a reminder of the fact that this department has often produced results of interest to the pharmacist. Not only was the early work on drug control carried on in the department which enforced the food and drug laws from 1906 until 1940, but the cultivation of drug plants has been one of its long-time research projects.

The bulletin mentioned above gives details regarding the cultivation, propagation, harvesting, drying, distillation of vital oils from, baling, packaging, storing, and marketing a long list of plants. Among these are aconite, arnica, belladonna, castor-bean, digitalis, henbane, licorice, mustard, stramonium, and valerian. In fact any drug plant that farmers might cultivate as a source of income interests the department.

During the recent unpleasantness the efforts of the department to get cinchona bark back home formed a dramatic story. As is well known the medicinal properties of the plant were discovered in Peru in the seventeenth century. Cinchona seed were originally obtained in South America by a British horticulturist, taken to England, and later turned over to the Dutch. They so improved the tree that they made Java the world's chief source of quinine. War with Japan cut us off from that source.

Twenty years earlier Col. Arthur F. Fischer, then head of the Philippine Bureau of Forestry, established cinchona growing in the Philippines. This in itself was a remarkable accomplishment as it involved obtaining seed of the high-yielding, carefully guarded *Cinchona ledgeriana* developed by the Dutch in Java.

In March 1942 Col. Fischer was ill of malaria in a field hospital of besieged Bataan and when he asked for more quinine there was hardly any. Though the Japanese already had control of most of the Philippine cinchona plantings, he knew of some trees still available at Mindanao. He flew there in an ancient plane and began

to collect bark. With makeshift equipment he prepared quinine from it.

Then Bataan fell. Mindanao's fall was imminent. Col. Fischer hurriedly collected about 2 million cinchona seeds, packed them in a milk can, and flew to Australia where Gen. MacArthur arranged for their shipment to Washington. Ultimately the seed reached the Department of Agriculture. Ordinarily relatively few of them would have grown and thrived in their native habitat, but the department's plant specialists had perfected seed germination in sphagnum moss.

Seed so grown escape the diseases that so severely damage them when planted in the soil. The Fischer cinchona seed went into sphagnum moss in greenhouses at Glenn Dale, Md., where they were fed with liquid nutrients and 90 percent of them responded by germinating. By the end of 1943 over 240,000 vigorous seedlings had been shipped by air to Brazil, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Mexico, Nicaragua, Peru, and Puerto Rico, with more to follow. In this way the quinine plant came back home and again flourishes in the Western Hemisphere.

Quite as dramatic a wartime story was the part department scientists played in the production of penicillin. This antibiotic had a curious history doubtless well known to the reader. It was discovered by chance and because the original discoverer and others reported difficulties in extracting it from the mold, *Penicillin notatum,* which produced it, it was given scant attention for a decade or more. Then the problem of isolating the antibiotic itself was solved in England but wartime made mass production impossible in the United Kingdom.

Here in its Northern Regional Reserach Laboratory at Peoria, Ill., the Department of Agriculture had the finest collection of useful and beneficial nonpathogenic organisms in existence. A brilliant chemist, Robert D. Cogill, headed the Fermentation Division. Dr. Charles Thom, a prominent mycologist, but recently retired from the department, went back to work again. Under their guidance that Fermentation Division became the focal point of penicillin development for the entire United Nations. A steady stream of specialists came to the Northern Laboratory from afar to learn techniques and methods.

The laboratory itself both discovered strains of the parent mold which produced the drug in greater quantity and developed a medium

upon which that mold grew more readily and produced the antibiotic in greater quantity. Species on hand and others drawn from distant places were tested. The addition of corn steep liquor, a by-product of the corn wet-milling process, increased the yield of penicillin tenfold. Better strains of the mold and improved production methods stepped this up a hundredfold. As the supply increased the price went down.

Ultimately the price of 100,000 units of penicillin was reduced from $20 to less than $1, and the current rate of production is about 125,000 times larger than in the first 6 months of 1943. Annual production has an estmiated value of 150 million dollars yet penicillin research by the Department of Agriculture cost only $100,000 alltold. The research was carried on in a laboratory that cost 2 million dollars. Whether presented in human or in economic terms the investment richly paid off. Physicians, pharmacists, hospitals, drug manufacturers, farmers, and the ill and injured all gained handsome dividends.

Streptomycin is another antibiotic produced at an agricultural research center to which the Federal Government contributes funds through the Department of Agriculture. Selman A. Waksman, a soil biologist at the New Jersey Agricultural Experiment Station, began to wonder whether some of the soil microorganisms might not produce antibiotics. He tested soils from all over the world and then tested the organisms under all manner of conditions.

Ultimately he came upon streptomycin. Soon various firms were erecting 20 million dollars worth of new plants in which to produce this antibiotic—a word coined by Dr. Waksman, incidentally. Yet the research was done in a laboratory operated with notable economy under the direction of a man on a relatively small salary. Production of streptomycin has now attained more than 2 million grams monthly and its price also has been reduced as the supply increased.

Department scientists have come upon a number of other interesting drugs in their work on agricultural by-product utilization. For instance there is subtilin, a product of a microorganism that grows on waste juices expressed during the commercial processing of asparagus, pears and citrus fruits. It is powerful and shows signs of being useful in treating pulmonary tuberculosis. The same can be said of usnic acid derived from Spanish moss.

Tomatin comes from the tomato plant. Just why the tomato plant needs this substance is its own private secret. It looks very useful in the treatment of human diseases causes by fungi, athlete's foot among them. An extract containing this antibiotic was first made from wilt-resistant tomtao plants at the department's Agricultural Research Center, Beltsville, Md. It has both antifungal and antibacterial properties.

Since then a crystalline material called tomatine has been isolated from this crude extract. Tomatine consists of two major fractions one of which is a basic alkaloid and the other essentially a mixture of sugars. It is the alkaloid which contains the antifungal properties and it has been named to tomatidine. So far the substance accountable for the antibacterial properties has not been isolated.

Polymyxin is an antibiotic that seems effective in brucellosis or so-called Bang's disease of cattle. It also is a mold product and is an outgrowth of the department's wartime research on synthetic rubber. Undulant fever is associated with Bang's disease and possibly polymyxin will be effective in that.

Gramacidin is a product of research by the California Medical School and the department's Western Regional Research Laboratory near San Francisco. In its original form it was too toxic for clinical test. But a modification is being devised that is soluble in water, weak enough to cause no toxic symptoms, and still strong enough to kill bacteria.

Workers at the Western Laboratory have also found in bran a fraction with antibiotic properties. It has some of the characteristics of a fatty acid and forms a water-soluble potassium salt or soap which has fairly high activity against *Staphyloccus aureus*, *Micrococcus conglomeratus*, and *Streptococcus faecalis*, but is inactive against *Escherichia coli*.

Finally James F. Couch and associates, who were so successful with rutin at the Eastern Regional Research Laboratory near Philadelphia, found a product in quercetin that possesses rather remarkable antibiotic properties on the acid side which it loses on the alkaline side. This activity is also lost in the presence of blood serum or iron. Quercetin is the yellow dye that appears when quercitron, the yellow coloring matter of black oak bark, is hydrolyzed with acid.

The story of rutin is quite recent and well known. First discovered in tobacco by James F. Couch and associates at the Eastern Laboratory, it was found to be effective in capillary fragility, and was later discovered in the buckwheat plant at a certain stage of growth. It can be prepared economically from either the green or the dried plant. At present 15 pharmaceutical houses are producing this drug, a research project which began with the chemical examination of tobacco plants to find possible industrial products.

Research on rutin cost approximately $300,000—also in a 2-million dollar laboratory. But it is expected that 50,000 acres will eventually be devoted to growing buckwheat plants from which to make the drug. Farmers alone should derive 2 million dollars annually from this acreage. If the raw material were all converted into leaf meal at $250 a ton, dehydrators would derive an income of 9 million dollars a year from the processing, and the rutin produced from the meal would have a value of 150 million dollars annually.

Another drug which progressed from haystack to sickrooms is dicumarol. As long as a century ago cattle growers and veterinarians observed that certain animals were frequently affected by fatal hemorrhagic disease. Then workers at the North Dakota Agricultural Experiment Station, as well as in Canada, discovered that the lethal bleeding was caused by the consumption of improperly cured clover hay or spoiled clover silage, and the condition began to be called sweet clover disease of cattle.

Next Karl Paul Link of the Wisconsin Agricultural Experiment Station conducted a brilliantly conceived series of studies which after 7 years culminated in the isolation and synthesis of the substance causing the condition. The Federal Government through the Department of Agriculture contributes financially to the work of all these State agricultural experiment stations.

The substance isolated was a tasteless, odorless, white crystalline powder at first called "dicumarin" and later dicumarol. The possibilties of using it as an anticoagulant were immediately appreciated and pharmaceutical and therapeutic studies began at once. This has resulted in widespread use of dicumarol as a complement to heparin used earlier for similar purposes. Oddly enough the structure of dicumarol is very like that of vitamin K (rutin closely resembles vitamin P) which is used to antagonize its effect.

Anticoagulant therapy with dicumarol has assumed great importance in a large group of diseases and the miracle of the haystack has won itself a permanent and an important place in the physician's armamentarium. Proper dosage reduces the clotting power of the blood and tends to prevent clot formation though it will not dissolve clots already formed.

There you have part of the continued story about the relationship between agricultural and pharmaceutical research and the Department of Agriculture and the corner pharmacy.

SELECTED ABSTRACTS

The Determination of Alkaloids by Ion Exchange. A. Jindra. *J. Pharm. and Pharmacol. 1*:87 (1949). The use of ion exchange for the quantitative analysis of chemical substances has been under study for some time. The author presents the results of a study to determine the effectiveness of artificial resins as adsorbents in the determination of alkaloids and of the alkaloidal content of galenicals.

The anion exchange resin Amberlite IR-4B was used as the adsorbing medium. The resin, in uniform grain size, was distributed in a glass tube to a height of about 5 cm. The solution was passed through the column at a rate of 90 to 120 drops per minute, with the exception of atropine sulfate which required a slower rate of about 30 to 40 drops per minute. The solvent used must be one in which both the alkaloidal salt and the free base are readily soluble.

An accurately weighed quantity of the alkaloidal salt was dissolved in 20 cc. of ethyl alcohol and adsorbed on the resin. The tube was then washed several times with a total of 50 cc. of warm ethyl alcohol to remove the adsorbed alkaloid base. The dissolved base was then determined by direct titration with N/10 hydrochloric acid, using a mixture of 10 drops of methyl red solution and 2 drops of methylene blue solution as the indicator. The color change was from green through blue to violet. The solvent used for morphine and quinine was methyl alcohol while ethyl alcohol was used for strychnine, atropine, brucine, ephedrine, and cinchonine. The determination of the alkaloidal content of galenicals was carried out using the same procedure. The solutions of the alkaloidal bases were colored and therefore, the equivalence point in the titration was determined electrometrically with a pH meter. The galenical solutions used were Tincture of Ipecac, Fld. Ext. of Cinchona, Tincture of Opium, and Tincture of Nux Vomica.

The results obtained with both the alkaloidal salts and the galenicals corresponded to theoretical results. An exception was the result with Tincture of Nux Vomica, where the result was always double the theoretical.

The author considers the advantages of this method to be its rapidity, simplicity, use of only small quantities of solvents, and the determination of all of the alkaloids present without any of the possibilities of loss arising from more complicated experimental procedures.

Pellet Implantation of Alpha Estradiol. H. M. Imerman. *West. J. Surg., Obst., Gynecol. 57*:29 (1949). Alpha estradiol is the most potent estrogenic hormone, being 80 times as potent as estriol and 12 times as potent as estrone. Each mg. of estradiol is equivalent to 120,000 I. U. The implantation of 25 mg. pellets of alpha estradiol has the advantage over other means of administration in that a sustained absorption and prolonged relief of symptoms is obtained. The author reported 22 cases having varying degrees of menopausal syndrome. Some of the patients were treated for premature menopause resulting from surgery and others for physiological menopause. All of the patients received treatment by pellet implantations and careful follow-up studies.

The pellets were implanted by means of a Kearns pellet injector into a site in the lower abdomen. A small amount of 1 per cent novocaine was infiltrated and the injector inserted. The pellet was then inserted into the subcutaneous tissue through the cannula by means of the plunger. After the injector was withdrawn a small dressing was applied since a suture was not usually necessary. The response to this treatment may be noted within 4 to 7 days. The sustained absorption and prolonged relief of symptoms eliminates frequent injections or the daily oral administration of estrogenic substances.

Importance of Vasoconstrictors in the Treatment of Maxillary Sinusitis. A. R. Everett. *N. Y. St. J. Med. 49*:417 (1949). The treatment of acute and chronic maxillary sinusitis with antibacterial agents has previously been rather disappointing in many respects. Agents such as sulfathiazole, sulfadiazine, tyrothricin, and penicillin did not give satisfactory results when instilled into the an-

trum followng irrigation, although their use in other parts of the body had indicated that they should be effective in the treatment of sinusitis. Then, a preparation containing 2.5 per cent sodium sulfathiazole and 0.125 per cent dl-desoxyephedrine hydrochloride was tried. The results were highly satisfactory, better than with any of the other agents used alone. Apparently the vasoconstrictor played a part in the effectiveness. Consequently, a 0.125 per cent solution of desoxyephedrine alone was instilled. The results in acute cases were superior than when penicillin alone was used.

A new preparation, the l-ephedrine crystalline salt of penicillin G, was tried by the author. This agent proved to be the most effective and the least toxic agent yet used in the treatment of acute and chronic maxillary sinusitis. The agent seemed to be particularly effective in chronic cases.

The author came to the conclusion that the presence of an effective, non-irritating vasoconstrictor, in sufficiently low concentration to avoid undesirable side effects, is essential in combination with antibiotic or chemotherapeutic agents in order to obtain consistently satisfactory results in the treatment of maxillary sinus infections. The author pointed out that this is not surprising when one considers the intense edema of the mucous membranes lining the sinuses during an infection. It has been shown that the capacity of the antrum may increase from 2 to 3 cc. during an infection to 12 to 15 cc. after resolution of the infection. The instillation of a solution containing a vasoconstrictor causes decongestion and shrinkage of the mucous membrane, thus exposing a greater surface area to the bactericidal agent.

Aureomycin Therapy of Rocky Mountain Spotted Fever. S. Ross, E. B. Schoenbach, F. G. Burke, M. S. Bryer, E. C. Rice, and J. A. Washington. *J. A. M. A. 138*:1213 (1948). The results of treatment of rickettsial infections in animals and the fact that human beings had been given doses of aureomycin up to 60 mg. per Kg. of body weight per day without toxic manifestations led the authors to treat 13 patients with the antibiotic. The infections of the patients were diagnosed clinically and serologically as the Eastern type Rocky Mountain Spotted Fever.

The usual oral dosage schedule was an initial 2 to 5 mg. per Kg. of body weight at hourly intervals for 3 doses with the interval then increased to two hours. In one case, however, the dose was as high as 12 mg. per Kg. of body weight. The dosage interval was usually changed to every 4 hours after the temperature had been normal for 48 hours. The shortest period of therapy was 4½ days and the longest was 9 days. The total amount of aureomycin administered ranged from 2.3 to 16.3 Gm. The authors pointed out that the optimum dose of the antibiotic was not determined in this study but that good clinical response may be expected from daily doses of 30 to 60 mg. per Kg. of body weight. No toxic manifestations were noted. The only side reactions were nausea and vomiting in 4 cases during the first 2 days of treatment.

In comparison with treatment of the disease with para-aminobenzoic acid, aureomycin was found to be superior for several reasons. There was a more dramatic return of the temperature to normal and patients were released from the hospital more quickly. The therapeutic response in the advanced cases was better than with PABA. The toxicity of aureomycin also seems to be less than that of para-aminobenzoic acid. Thus, since there was striking improvement in all of the patients in this series it would seem to indicate that aureomycin is an effective agent in the treatment of Rocky Mountain Spotted Fever.

Treatment of Primary Atypical Pneumonia With Aureomycin. E. B. Schoenbach and M. S. Bryer. *J. A. M. A. 139:275* (1949). Primary atypical pneumonia is a disease resembling similar pulmonary infections of bacterial, viral, or rickettsial origin but from which no causative agent has been isolated. However, sputum from patients suffering with the disease has been shown to be able to incite the disease in other human beings. Diagnosis is based upon clinical symptoms and the elimination of other bacterial, viral or rickettsial agents which would cause the pulmonary consolidation shown by roentgenological examination.

Thirteen consecutive patients with atypical pneumonia were treated with aureomycin and all manifested a striking clinical response soon after therapy was begun. The authors felt that the probability

that this response was purely coincidental was remote. All but one of the patients were severely ill and 9 had received penicillin or sulfadiazine previously in doses that would normally be considered adequate.

The aureomycin was administered orally in an initial dose of 30 to 50 mg. per Kg. of body weight per day. Usually the schedule was to administer 100 to 250 mg. of the antibiotic every hour for 3 doses and then the same dosage every 2 hours until the patients became afebrile. Thereafter, the aureomycin was given every 4 to 6 hours for 2 to 5 days in an amount of 15 to 20 mg. per Kg. Nine of the patients were afebrile within 24 hours of the institution of therapy.

The antibiotic was well tolerated by the patients in this series. Nausea was present in 6 patients before treatment with aureomycin. This abated with therapy and no nausea occurred in the other patients. Mild drowsiness was noted by several of the patients but no neurologic or other abnormalities were noted.

Penicillin or Silver Nitrate as a Prophylactic Against Ophthalmia Neonatorum? C. Berens and F. M. Foote. *Am. J. Public Health 38*:1680 (1948). The question of whether or not penicillin should be used in place of the time honored treatment with silver nitrate for the prevention of ophthalmia neonatorum is discussed by the authors. They refer to the chief work reported on prophylaxis with penicillin as carried out by Franklin of the U. S. Public Health Service. A total of 2,138 infants was treated with a sterile isotonic sodium chloride solution containing 2,500 units of sodium pencillin per cc. Four instillations were used at first but later reduced to one instillation. No case of conjunctivitis caused by the gonococcus was noted but a few cases caused by staphylococcus developed. However, the authors pointed out that this work was instructive but not statistically significant.

They then discuss the effectiveness of 1 or 2 per cent silver nitrate solution. During 1947, 57 professors of obstetrics reported 112,035 births in their services. Only 67 cases of ophthalmia neonatorum occurred in this group and many of these were not due to gonococci. There was no damage from silver nitrate among these 112,035 live

births. The years of usefulness have proven that there is no evidence that permanent damage results from the use of 1 or 2 per cent silver nitrate.

The authors cite a report by the Council of the American Academy of Ophthalmology and Otolaryngology and the Section on Ophthalmology of the A. M. A. which recommended that no changes be made in the existing laws. It stated that, although some form of antibiotic prophylaxis may eventually replace the use of silver nitrate, much further investigation is needed before concrete recommendations can be made.

The Use of Antihistaminic Drugs in the Treatment of the Common Cold. John M. Brewster. *U. S. Nav. Med. Bull. 49*:1 (1949). Because of the similarity of the symptoms of the common cold to those of hay fever and because of the phenomenal cure of early colds with the antihistaminics it is believed that colds are allergic reactions. In the study reported by the author several antihistaminic drugs were employed, i. e., Pyribenzamine, Benadryl, Neoantergan, Thenylene, and Histadyl. All were equally effective in curative value and all produced some degree of drowsiness as the principal side reaction. Neoantergan produced the least drowsiness and was therefore the favorite among the patients having experience with more than one of the drugs.

The antihistaminics were administered in doses of 50 mg. with instructions to the patient to repeat the dose at least 3 times at 4-hour intervals. If symptoms persisted the doses should be continued. As a control 16 mg. each of codeine sulfate and papaverine hydrochloride were administered on the same schedule.

In the series of 572 patients treated it was found that the effectiveness of treatment varied inversely with the lapse of time between the onset of symptoms and the beginning of therapy. When treatment with the antihistaminic drugs was begun within the first hour after the onset of symptoms 19 of 21 were cured, within 2 hours 48 of 55 were cured, within 6 hours 116 of 156 were cured, and within 12 hours 165 of 234 were cured. Among the 77 patients used as controls there were 14 of 34 who were treated within 12 hours who were cured, but none of those receiving treatment after 24 hours were cured. In most of the patients who began treatment

with the antihistaminics too late to have their colds aborted there was a shortening of the duration to 3 to 5 days and a marked reduction in the intensity of symptoms and the development of complications. There were no instances of severe side reactions or toxemia. Those receiving treatment during the day were often given 2.5 to 10 mg. of amphetamine to counteract the drowsiness.

The author concluded that if the antihistaminics were properly and universally prescribed the incidence of common colds could be reduced to near the vanishing point.

BOOK REVIEWS

Review of Pharmacy. By George W. Fiero. Sixth Edition, 121 pages including index. John Wiley & Sons, Inc., New York. 1949. Price $3.00.

This brief work is a condensation of certain essential facts pertaining to the drugs of the United States Pharmacopeia, Thirteenth Revision and the National Formulary, Eighth Edition. It is in essence an outline of names, strengths, doses, composition, etc. which might prove useful to the student who has difficulty in remembering factual data. Its use as a reference is limited by its brevity and its restricted scope.

We do not question its likely value for those who are preparing for the purely "memory test" which once was called an examination but we doubt if the modern type of examination would make its use for preparation feasible. The suggestion that the subject of pharmacy can be reviewed within the space of 120 pages is not in line with the expansion which pharmacy has taken in the last decade. Your reviewer considers this book a projection of those days when the teaching of pharmacy was largely on a question and answer basis. For those interested in such study and this kind of examination preparation it has some use.

The National Formulary. The British Medical Association and The Pharmaceutical Society of Great Britain. 128 pages. The Pharmaceutical Press, 17 Bloomsbury Sq., London W. C. 1; 1949. Price 2.6d, interleaved 4.0.

This small volume is the result of work by a joint Formulary Committee made up of representatives of the British Medical Association, the Pharmaceutical Society of Great Britain and a number of government ministries. Its purpose is to supply a convenient pocket size volume, for use by the physician and pharmacist, which will provide a standard group of preparations for the prescribing physician. This was done in an effort to develop greater uniformity

in the formulas prescribed and to increase efficiency. It is hoped that fewer hospitals will issue their own formulary, using this instead.

The formulas are divided into groups according to their manner of use, thus capsules, collyria, creams, etc., and each is given in Imperial and metric quantities.

Few data are given concerning basic drugs since it is not the intent of this work to give such material. The formulas are interesting to American pharmacists for it is likely that our English pharmacists dispense their own preparations more often than is the case here.

Future revisions of this Formulary are planned in order to keep it in accordance with the prescribing practice of the time.

How to Become a Doctor. By George R. Moon. Examiner and Recorder, University of Illinois Colleges of Medicine, Dentistry and Pharmacy. 131 pages. The Blakiston Co., Philadelphia and Toronto. Price $2.00.

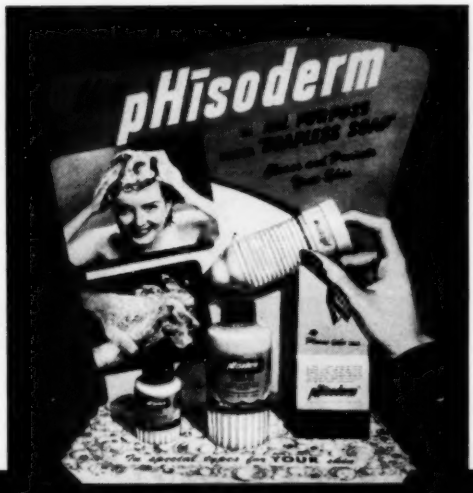
This is a most unusual book and one that should be read carefully by every boy or girl planning to enter any one of the health professions. If it were so read many would be spared difficulties and disappointment and both candidates for admission to professional schools as well as school administrators would have fewer problems.

The book describes in clear, concise language the problems faced by each person who seeks admission to medical school, starting with the proper type of premedical education, the selection of a medical school, the application, the personal interview, entrance examinations, tuition and other costs, etc. Many of the personal problems while in medical school are explained such as working, marriage and housing. Internship and residencies are discussed and good advice is given on such problems.

The other health professions are similarly considered, although not in quite as much detail. Approved schools in all branches are listed with their location and approximate fees.

Your reviewer is of the opinion that this book is extremely valuable to both prospective students and all persons engaged in student counseling and guidance. Its author writes with clarity and with an obvious wealth of experience and he is to be commended.

We predict that "How to Become a Doctor" will be well received and widely sold at its very reasonable price.



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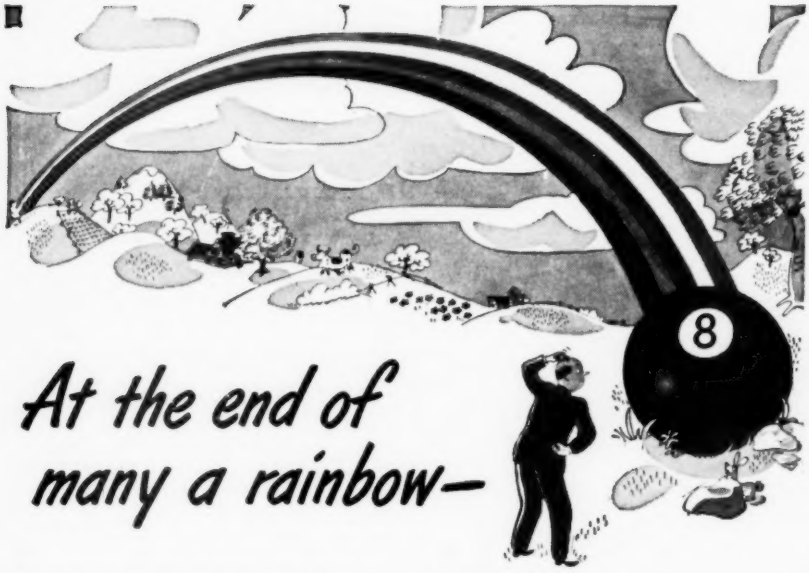

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